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Nitrone Cycloaddition Route to the 1β-Methylcarbapenem Key Intermediate[1,2]

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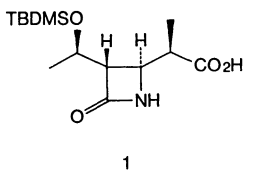
The 1β-methylcarbapenem key intermediate, (3*S*,4*S*)-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-4-[(*R*)-1-carboxyethyl]-2-azetidinone, was prepared from (*S*)-methyl 3-hydroxy-2-methylpropionate by employing 1,3-dipolar cycloaddition of the chiral nitrone with benzyl crotonate as a key reaction.

Since its development first by Kametani[3,4] and later by Stevens,[5] the nitrone cycloaddition route has been recognized as one of the most reliable methods of preparing several structural types of carbapenem key intermediates.[4] The preparation of optically active carbapenem key intermediates has been also accomplished by the same methodology which utilizes the chiral nitrones derived from (*R*)-(+)-*N*-(α-phenylethyl)hydroxylamine[6] or (−)-menthyl glyoxylate hydrate.[7]

Based on these successful results so far reported,[3-7] we examined to explore the nitrone cycloaddition route for preparing the optically active 1β-methylcarbapenem key intermediate (**1**). The novel nitrone (**2**) obtainable from commercially available (*S*)-methyl 3-hydroxy-2-methylpropionate (**3**), was employed as a dipole by expecting that the chiral center involved in **2** may control the steric course of addition reaction in a



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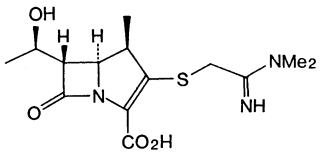

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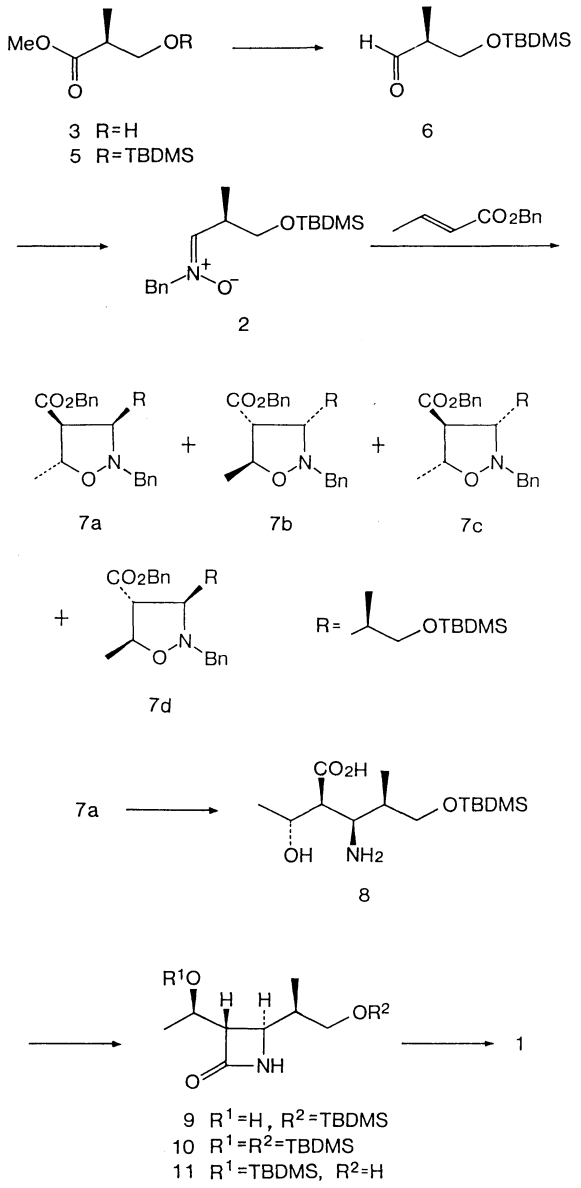
desired sence. The 1β-methylcarbapenem such as **4** is currently well-known as the synthetic carbapenem antibiotic showing excellent antibacterial activity, chemical stability, and insensitivity to renal dipeptidase-I.[8] We wish to report here that, while the control of steric course of cycloaddition reaction is not realized contrary to our expectation, the synthetic scheme can really produce optically pure **1** starting from **3**.

As shown in Scheme 1, sequential silylation of **3** and reduction of the methyl ester (**5**) gave the chiral aldehyde (**6**) in a good combined yield. Treatment of **6** with benzylhydroxylamine[9] produced a 64% yield of the optically active nitrone (**2**). The cycloaddition of **2** with benzyl crotonate was effected by heating 80 °C in toluene, producing the adduct (**7**) in 80% yield. Disappointingly, the 400 MHz NMR spectrum of **7** clearly disclosed that it consisted of almost the same amounts of four possible diastereomers (**7a—d**) in a ratio of 21:29:23:27. This represents that the endo- and exo-additions occur in an almost equal probability and the chiral center of **2** originating from **3** can not control the steric course of addition reaction. The diastereoselectivity could not be improved in favor of the desired diastereomer (**7a**) even by employing various crotonic acid esters and amides and



several solvent systems. Accordingly, the selective hydrolysis of **7a—d** was next examined by expecting that the ester groups of the useless $C_{3,4}$-trans adducts (**7c,d**) should be more rapidly saponified than those of the sterically congested $C_{3,4}$-cis isomers (**7a,b**). As expected, when the mixture of **7a—d** was treated with aq barium hydroxide in tetrahydrofuran[10] and the ester mixture (**7a—d**) obtained in 55% recovery was analyzed by 400 MHz NMR spectrum, the ratio of **7a—d** was found to be improved to 34:20:5:41. These results definitely suggest that the orginal reaction product (**7a—d**) contains the $C_{3,4}$-cis- and the $C_{3,4}$-trans-isomers (**7a,b** and **7c,d**) in a ratio of 48(21+27):52(29+23) and the partial saponification increases the ratio of **7a,b** to **7c,d** to 75(34+41):25(20+5).

Since the separation of **7a—d** turned out to be fruitless, the preparation of the optically active β-amino acid (**8**) was attempted by using the ester mixture in which the fraction of **7a** had been enriched. Treatment of **7a—d** under hydrogenolysis conditions followed by careful separation with column chromatography gave **8** from the major fraction in 21% yield,[11] mp 178—179 °C (decomp) and $[\alpha]_D^{20}$ −2.0° (methanol). Although it was quite ambiguous whether the isolated β-amino acid involves the desired stereochemistry, **8** was rigorously verified by obtaining the alcohol (**11**) from this compound.

The optically active β-amino acid (**8**) was lactamized by the Mukaiyama-Ohno method,[12] giving the lactam (**9**) in a quantitative yield, mp 105—106 °C and $[\alpha]_D^{20}$ −8.6° (chloroform). Studies on the ^{1}H NMR spectrum measured in the presence of the chiral shift reagent (Eu(hfc)$_3$) clearly disclosed that each synthetic step to the stage of **9** can proceed without substantial racemization (see Experimental.) Introduction of a *t*-butyldimethylsilyl group into the secondary alcohol of **9**, followed by selective acidic removal of the *t*-butyldimethylsilyl group which protects the primary alcohol of **10**, produced the optically pure alcohol (**11**) in 79% overall yield, mp 89—90 °C and $[\alpha]_D^{20}$ −20.9° (chloroform). This was identified with the authentic sample[13] by spectral comparisons. It has already been established that oxidation of **11** with pyridinium dichromate can produce **1** in 91% yield.[13]

As described above, we have succeeded in developing the new synthetic route to optically pure **1** by featuring the nitrone cycloaddition as a key reaction. The overall scheme may have a practical value if the diastereoselectivity of the addition reaction could be much more improved.

Experimental

General. All melting points were determined with a Yamato MP-21 melting point apparatus and were uncorrected. IR spectral measurements were carried out with a JASCO A-202 diffraction grating infrared spectrometer. ^{1}H NMR spectra were recorded with a Hitachi R-90H spectrometer (90 MHz) and a Bruker AM-400 spectrometer (400 MHz). All signals were expressed as ppm downfield from TMS used as an internal standard (δ value). Mass spectra were taken with a Hitachi RMU-6MG mass spectrometer. Measurements of optical rotations were performed with a Horiba SEPA-200 automatic digital polarimeter. Wakogel C-200 was used as an adsorbent for column chromatography.

(*S*)-(+)-Methyl 3-(*t*-Butyldimethylsilyloxy)-2-methylpropionate (5). *t*-Butyldimethylchlorosilane (1.30 g, 8.6 mmol) was added to a solution of commercially available **3** (1.00 g, 8.5 mmol) and imidazole (1.15 g, 17 mmol) in DMF (10 mL) at rt and the mixture was stirred there for 1.5 h. After H_2O (10 mL) and hexane (20 mL) were added to the reaction mixture, the organic layer was separated and the aqueous layer was extracted with hexane. The combined organic layers were washed with water and dried over anhyd $MgSO_4$. Filtration and concentration in vacuo gave **5** as a colorless oil (1.91 g, 97%). Bulb-to-bulb distillation (120 °C, 14 mmHg†) afforded an analytical sample of **5**. $[\alpha]_D^{20}$ +18.9° (*c* 1.00, $CHCl_3$). IR (neat) 2950, 2860, 1740, 1460, 1255, 1196, 1173, 1096, 833, 775 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=0.03 (6H, s, Me_2Si), 0.87 (9H, s, Me_3CSi), 1.13 (3H, d, *J*=7.0 Hz, MeCH), 2.64 (1H, m, MeCH), 3.66 (3H, s, COOMe), 3.60—3.80 (2H, m, CH_2O). MS *m/z* 217 $[M-Me]^+$, 201 $[M-MeO]^+$, 175 $[M-t\text{-}Bu]^+$.

(*S*)-(+)-3-(*t*-Butyldimethylsilyloxy)-2-methylpropanal (6). A one mol dm^{-3} solution (8.4 mL) of diisobutylaluminium hydride in hexane was added to a stirred solution of **5** (1.31 g, 5.6 mmol) in Et_2O (18.5 mL) over 5 min at −78 °C. After the stirring was continued at the same temperature for 30 min, the reaction mixture was diluted successively with MeOH (0.09 mL) and H_2O (0.84 mL). The resulting gelatinous mixture was filtered and washed with Et_2O. The filtrate was dried over anhyd $MgSO_4$, concentrated in vacuo, then purified with column chromatography (SiO_2: hexane–EtOAc 9:1), giving **6** as a colorless oil (0.890 g, 78%). Bulb-to-bulb distillation (110 °C, 14 mmHg) gave an analytical sample of **6**. $[\alpha]_D^{20}$ +37.8° (*c* 1.20, $CHCl_3$). IR (neat) 2950, 2860, 1735, 1470, 1256, 1100, 1029, 835, 777 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=0.00 (6H, s, Me_2Si), 0.82 (9H, s, Me_3CSi), 1.04 (3H, d, *J*=7.0 Hz, MeCH), 2.50 (1H, m, MeCH), 3.78 (2H, d, *J*=5.9 Hz, CH_2O), 9.74 (1H, d, *J*=1.5 Hz, CHO).

(*R*)-(−)-*N*-(3-*t*-Butyldimethylsilyloxy-2-methylpropylidene)benzylamine *N*-Oxide (2). The aldehyde (**6**) (0.600 g, 3.0 mmol) was added dropwise to a mixture of *N*-benzylhydroxylamine[9] (0.368 g, 3.0 mmol) and $CaCl_2$ (0.330 g, 3.0 mmol) in Et_2O (30 mL) at 0 °C. The stirring was continued there for 1 h and at rt for 2 h. After being filtered, the reaction mixture was concentrated in vacuo. The concentration residue was purified with column chromatography (SiO_2: hexane–EtOAc 1:1—0:1) to give **2** as a colorless oil (0.658 g, 64%). $[\alpha]_D^{20}$ −37.7° (*c* 0.89, $CHCl_3$). IR (neat) 2950, 2870, 1595, 1460, 1256, 1098, 840, 780, 702 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=−0.02, 0.00 (6H, two s, Me_2Si), 0.84 (9H, s, Me_3CSi), 1.10 (3H, d, *J*=6.8 Hz, MeCH), 3.10—3.40 (1H, m, MeCH), 3.63 (2H, m, CH_2O), 4.87 (2H, s, $PhCH_2$), 6.59 (1H, d, *J*=7.0 Hz, CH=N), 7.37 (5H, s, C_6H_5). MS *m/z* 307 $[M]^+$, 292 $[M-Me]^+$, 290 $[M-OH]^+$, 250 $[M-t\text{-}Bu]^+$. Found:

† 1 mmHg=133.322 Pa.

C, 65.86; H, 9.25; N, 4.46%. Calcd for $C_{17}H_{29}NO_2Si$: C, 66.40; H, 9.51; N, 4.55%.

Cycloaddition of (*R*)-(−)-*N*-(3-*t*-Butyldimethylsilyloxy-2-methylpropylidene)benzylamine *N*-Oxide (6) with Benzyl Crotonate. Preparation of a Mixture of the Four Diastereomers of 2-benzyl-4-benzyloxycarbonyl-3-[(*R*)-2-*t*-butyldimethylsilyloxy-1-methylethyl]-5-methylisoxazolidine (**7a—d**). Benzyl crotonate (0.89 g, 5.6 mmol) was added to a solution of **5** (0.86 g, 2.8 mmol) in anhyd toluene (2.8 mL) and the mixture was stirred at 80 °C for 24 h. After toluene and excess benzyl crotonate were distilled off at 110 °C in vacuo, the oily residue was purified with column chromatography (SiO_2: hexane–EtOAc 19:1), giving a mixture of **7a—d** as a colorless oil (1.03 g, 80%). IR (neat) 2950, 2880, 1738, 1454, 1255, 1178, 1090, 837, 777, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ=−0.053, −0.046, −0.036, −0.029, −0.021, 0.005, 0.014 (6H, seven s, Me_2Si, intensity ratio: 12:23:14:12:14:14:11), 0.836, 0.839, 0.873 (9H, three s, Me_3CSi intensity ratio: 22:52:26), 1.33, 1.34, 1.35, 1.36 (3H, four d, *J*=6.07, 5.86, 5.81, and 6.03 Hz, MeCHCH$_2$O intensity ratio: 21:29:23:27), 1.65—2.05 (1H, m, MeCH CH$_2$O), 2.70—4.42 (6H, other protons) 4.40—4.66 (1H, m, MeCHO), 5.10—5.50 (2H, m, PhCH$_2$O), 7.20—7.42 (10H, m, aromatic protons). Based on the NMR spectrum, the formation ratio of **7a—d** could be estimated as 21:29:23:27. Since several attempts to separate **7a—d** turned out to be fruitless, the assignment of NMR signals and the determination of chemical yield for each diastereomer could not be achieved. However, comparison of the NMR spectra of the mixture of **7a—d** before and after saponification rigorously uncovered the formation ratio of the $C_{3,4}$-cis isomers (**7a,b**) to the $C_{3,4}$-trans ones (**7c,d**) as 48(21+27):52-(29+23). MS *m/z* 483 $[M]^+$, 468 $[M-Me]^+$, 426 $[M-t\text{-}Bu]^+$.

Selective Saponification of the Mixture of the Four Diastereomers of 2-Benzyl-4-benzyloxycarbonyl-3-[(*R*)-2-*t*-butyldimethylsilyloxy-1-methylethyl]-5-methylisoxazolidine (7a—d). Satd aq $Ba(OH)_2$ (50 mL) was added to a solution of the four diastereomers mixture of **7** (5.50 g) in THF (50 mL) and the mixture was stirred vigorously at the same temperature for 24 h. After an insoluble material was removed by filtration, the filtrate was diluted with hexane (150 mL). The upper organic layer was separated, washed successively with satd aq $NaHCO_3$, satd NaCl, then dried over anhyd $MgSO_4$. Filtration and concentration in vacuo gave an oily residue which was purified with column chromatography (SiO_2, hexane–EtOAc 1:0→19:1) to give a mixture of **7a—d** (3.00 g, 55% recovery). ^1H NMR ($CDCl_3$, 400 MHz) δ=−0.053, −0.046, −0.036, −0.029, −0.021, 0.005, 0.014 (6H, seven s, Me_2Si, intensity ratio: 17:11:20:4:8:23:17), 1.33, 1.34, 1.35, 1.36 (3H, four d, *J*=6.07, 5.86, 5.81, and 6.03 Hz, intensity ratio: 34:20:5:41). Since the $C_{3,4}$-trans isomers (**7c,d**) was expected to be saponified more preferencially than the $C_{3,4}$-cis ones (**7a,b**), this selective saponification could improve the ratio of the latter isomers to the former ones (**7a,b**:**7c,d**) from 48:52 to 75:25.

(2*S*,3*R*,4*R*)-3-Amino-5-*t*-butyldimethylsilyloxy-2-[(*R*)-1-hydroxyethyl]-4-methylpentanoic Acid (8). 10% Palladium on carbon (1.00 g) was added to a methanolic solution (50 mL) containing **7a—d** (10.0 g, 20.7 mmol) directly obtained by the above selective saponification, and the whole mixture was stirred under a hydrogen atmosphere (5 atm) for 7 h. The catalyst was filtered off and the filtrate was concentrated in vacuo. The concentration residue was purified by column chromatography (SiO_2: $CHCl_3$–MeOH 10:1→8:1) to give **8** as a colorless solid (1.30 g, 21%)[11] from the major fraction. Recrystallization of **8** from EtOH–H_2O (1:2) gave an analytical sample of **8** as colorless needles, mp 178—179 °C (decomp.) and $[\alpha]_D^{20}$ −2.0° (*c* 1.18, MeOH). IR (KBr) 3500, 2900, 2120, 1640, 1540, 1480, 1405, 1340, 1284, 1258, 1198, 1126, 1100, 1080, 1055, 1005, 960, 840, 813, 782, 728, 680, 620, 594, 557, 474 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.06 (6H, s, Me_2Si), 0.89 (9H, s, Me_3CSi), 1.12 (3H, d, *J*=7.0 Hz, MeCHCH$_2$O), 1.23 (3H, d, *J*=6.4 Hz, MeCHO), 1.95 (1H, m, MeCHCH$_2$O), 2.51 (1H, m, CHCOOH), 3.69 (3H, m, MeCHCH$_2$ and CHNH$_2$), 4.21 (1H, m, MeCHO). MS *m/z* 290 $[M-Me]^+$, 260 $[M-COOH]^+$, 248 $[M-t\text{-}Bu]^+$. Found: C, 54.81; H, 10.26; N, 4.48%. Calcd for $C_{14}H_{31}NO_4Si$: C, 55.04; H, 10.23; N, 4.59%.

(3*S*,4*R*)-4-[(*R*)-1-(*t*-Butyldimethylsilyloxymethyl)ethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone (9). A solution of triphenylphosphine (1.01 g, 3.9 mmol) in acetonitrile (62 mL) was added dropwise to a solution of recrystallized **8** (0.980 g, 3.2 mmol) and di-2-pyridyl disulfide (0.850 g, 3.9 mmol) in acetonitrile (300 mL) under reflux. After the heating at reflux was continued for 3 h, the mixture was concentrated in vacuo and the residue was dissolved in ether (40 mL). The ethereal solution was washed successively with 1 mol dm^{-3} NaOH and satd NaCl, then dried over anhyd Na_2SO_4. After filtration and concentration in vacuo, the residue was dissolved in EtOAc (3.7 mL). The ethyl acetate solution was diluted with hexane (8.9 mL) to crystallize triphenylphosphine oxide. After filtration, the filtrate was concentrated in vacuo to give almost pure **9** as a colorless solid (0.970 g, quantitative yield). A part of the residue was purified with TLC (SiO_2: hexane–EtOAc 3:7) and recrystallized from benzene, affording an analytical sample as colorless crystals, mp 105—106 °C and $[\alpha]_D^{20}$ −8.6° (*c* 1.08, $CHCl_3$). IR (KBr) 3370, 3230, 2950, 2870, 1722, 1475, 1363, 1314, 1255, 1154, 1089, 997, 840, 777, 708, 684 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.09 (6H, s, Me_2Si), 0.91 (9H, s, Me_3CSi), 0.96 (3H, d, *J*=6.8 Hz, MeCHO), 1.34 (3H, d, *J*=6.4 Hz, MeCHCH$_2$O), 1.77 (1H, m), 2.73 (1H, d, *J*=4.6 Hz, MeCHOH), 3.01 (1H, dd, *J*=7.8, 2.0 Hz, CHNH), 3.51 (1H, dd, *J*=7.8, 2.0 Hz, CHCO), 3.62 (2H, m, MeCHCH$_2$O), 4.14 (1H, m, MeCHO), 5.95 (1H, bs, NH). MS *m/z* 272 $[M-Me]^+$, 270 $[M-OH]^+$, 259 $[M-Me-OH]^+$, 230 $[M-t\text{-}Bu]^+$. Found: C, 58.71; H, 10.00; N, 4.87%. Calcd for $C_{14}H_{29}NO_3Si$: C, 58.49; H, 10.17; N, 4.87%. In order to examine an extent of racemization to the stage of **9** in the synthetic scheme, another lot of **9** (21.0 mg, 20%) was prepared from the mixture of **7a—d** (175 mg, 0.36 mmol) without any recrystallizations according to the reaction steps described above. Measurement of the ^1H NMR spectrum carried out with this sample in the presence of the chiral shift reagent [Eu(hfc)$_3$] clearly showed the methyl group of MeCHCH$_2$O moiety in an intensity ratio of 97.5:2.5 as two doublets at 1.82 and 1.79 ppm. Since the racemic β-lactam (*dl*-**9**)[14] exhibited the same methyl group as two sets of doublets of equal intensity at 1.79 and 1.82 ppm, the optical purity of **9** was estimated 95%ee. Accordingly, it became evident that each synthetic step to the stage of **9** could proceed without substantial racemization.

(3*S*,4*R*)-4-[(*R*)-1-(*t*-Butyldimethylsilyloxymethyl)ethyl]-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (10). *t*-

Butyldimethylchlorosilane (35.0 mg, 0.23 mmol) was added to a solution of **9** (22.4 mg, 0.078 mmol) and imidazole (32.0 mg, 0.47 mmol) in DMF (0.5 mL) and the mixture was stirred at rt for 1.5 h. After the reaction was quenched by adding H_2O (0.5 mL), the mixture was extracted with EtOAc. The combined extracts were washed with H_2O, dried over anhyd $MgSO_4$, filtered, then concentrated in vacuo. The residue was purified with column chromatography (SiO_2: hexane–EtOAc 9:1→17:3) to give **10** as colorless crystals (31.1 mg, 99%). Recrystallization from MeOH–H_2O gave an analytical sample of **10** as colorless crystals, mp 97—99 °C and $[\alpha]_D^{20}$ −6.7° (*c* 0.95, $CHCl_3$). IR (KBr) 3470, 3180, 3120, 2950, 2880, 1760, 1717, 1480, 1258, 1140, 1101, 968, 840, 780 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.04, 0.07 (12H, two s, Me_2Six2), 0.87, 0.89 (18H, two s, Me_3CSix2), 0.96 (3H, d, *J*=6.8 Hz, MeCHCH$_2$O) 1.22 (3H, d, *J*=6.4 Hz, MeCHO), 1.79 (1H, m, MeCHCH$_2$), 2.88 (1H, m, CHNH), 3.55 (2H, d, *J*=4.8 Hz, MeCHCH$_2$), 3.70 (1H, dd, *J*=5.4, 2.3 Hz, CHCO), 4.17 (1H, dq, *J*=6.4, 5.4 Hz, MeCHO), 5.74 (1H, bs, NH). MS *m/z* 386 $[M-Me]^+$, 344 $[M-t\text{-Bu}]^+$. Found: C, 59.84; H, 10.71; N, 3.41%. Calcd for $C_{20}H_{43}NO_3Si_2$: C, 59.80; H, 10.79; N, 3.49%.

(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(*R*)-1-(hydroxymethyl)ethyl]-2-azetidinone (11). One mol dm^{-3} hydrochloric acid (4.0 μL) was added to a solution of **10** (10.7 mg, 0.027 mmol) in MeOH (1.0 mL) and H_2O (0.2 mL) at 0 °C and the mixture was stirred there for 2 d. After satd aq $NaHCO_3$ (0.5 mL) and satd NaCl (1.0 mL) were added, the mixture was extracted with EtOAc. The combined organic extracts were washed with satd NaCl, dried over anhyd $MgSO_4$, filtered, then concentrated in vacuo. The residual solid was purified with column chromatography (SiO_2: hexane–EtOAc 1:1) to give **11** (6.1 mg, 80%) as colorless crystals, mp 89—90 °C and $[\alpha]_D^{20}$ −20.9° (*c* 0.37, $CHCl_3$) (lit.,[11] mp 90—91 °C and $[\alpha]_D^{20}$ −21.7° (*c* 0.46, $CHCl_3$)). IR (KBr) 3450, 3180, 3100, 2950, 1755, 1713, 1373, 1255, 1140, 1098, 1062, 1050, 1027, 984, 963, 838, 810, 780 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.13 (6H, s, Me_2Si), 0.90 (3H, d, *J*=6.8 Hz, MeCHCH$_2$O), 0.92 (9H, s, Me_3CSi), 1.35 (3H, d, *J*=6.0 Hz, MeCHO), 1.86 (1H, m, MeCHCH$_2$O), 2.96 (1H, dd, *J*=8.3, 4.9 Hz, OH), 3.15 (1H, ddd, *J*=9.0, 2.2, 1.0 Hz, CHN), 3.30 (1H, dd, *J*=8.8, 2.2 Hz, CHCO), 3.53 (2H, m, CH$_2$OH), 4.13 (1H, dq, *J*=8.8, 6.0 Hz, MeCHO), 5.99 (1H, bs, NH). MS *m/z* 272 $[M-Me]^+$, 230 $[M-t\text{-Bu}]^+$. These spectral properties were identical with those of the authentic sample independently prepared by our hands.[13] Found: C, 58.30; H, 10.15; N, 4.75%. Calcd for $C_{14}H_{29}NO_3Si$: C, 58.49; H, 10.17; N, 4.87%.

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References

1) A part of this work has been published in a form of the patent. S. Terashima, Y. Kimura, Y. Ito, K. Sakai, and T. Hiyama, Japan Kokai Tokkyo Koho JP 62-29577 (1987).

2) After completion of this work, the same synthetic scheme to **1** as that reported herein has been reported by Kametani et al. They have also disclosed that the isoxazolidine derivative of desired stereochemistry can be obtained as a sole product by the intramolecular version of the cycloaddition reaction. The 107th Annual Meeting of the Pharmaceutical Society of Japan, Kyoto, April, 1987. Abstract Paper, p. 271.

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10) When aq sodium hydroxide or aq potassium hydroxide solution was employed in place of aq barium hydroxide solution and alcoholic solvents were used as the reaction medium, significant epimerization of the C_4 esters of the $C_{3,4}$-cis-adducts (**7a,b**) was observed.

11) In another hydrogenolysis carried out in a small scale, we have succeeded in obtaining the other two diastereomers of **8** in pure states by TLC separation (SiO_2, $CHCl_3$–MeOH 6:1) although their yields could not be specified. When being treated under the Mukaiyama–Ohno conditions,[12] these two compounds were found to produce the *trans*- and the *cis*-β-lactams whose stereochemistry could be definitely determined by NMR analyses. Accordingly, the diastereomers of **7** which gave the *trans*-β-lactam was identified as **7b** and the other producing the *cis*-β-lactam as **7c** or **d** (Y. Ito, Y. Kimura, and S. Terashima, unpublished results).

12) M. Ohno, S. Kobayashi, T. Iimori, Y.-F. Wang, and T. Izawa, *J. Am. Chem. Soc.*, **103**, 2405 (1981).

13) T. Kawabata, Y. Kimura, Y. Ito, S. Terashima, A. Sasaki, and M. Sunagawa, *Tetrahedron Lett.*, **27**, 6241 (1986).

14) The racemic β-lactam (*dl*-**9**) was prepared from racemic 3-(*t*-butyldimethylsilyloxy)-2-methylpropanal according to the same synthetic route as that reported for optically active **9** (Y. Ito, Y. Kimura, and S. Terashima, unpublished results).